Remarks

Claims 1-100, 123-131 and 134 were previously canceled.

Claims 101-122, 132-133, and 135-136 are pending and amended as discussed below. Claim 101 is now clearly drawn to a method for administration of a nanoparticulate formulation to the CNS; claim 102 to a method of making this nanoparticulate formulation for administration of drug to the CNS. Support for these amendments are found in the specification at page 6, lines 18-24.

Rejections Under 35 U.S.C. § 102

Claims 101-108, 111-122, 132, and 133 were rejected under 35 U.S.C. § 102(a) as disclosed by Reszka, et al., J. Pharmacology and Experimental Therapeutics 280(1): 232-237 (1/1997) ("Reszka") or Beck, et al., Microencapsulation 10(1):101-114 (1993) ("Beck"). Applicants respectfully traverse these rejections to the extent that they are applied to the claims as amended.

a. Reszka

Reszka describes the use of three compositions: (1) liposomes; (2) polybutylcyanoacrylate (PBCA) nanoparticle which were prepared by emulsion polymerization using 1% butylcyanoacrylate monomer, 1% dextran 70 and 0.2% polyoxamer 188 in 0.01 N HCl; and (3) PBCA nanoparticles coated with 1% poloxamine, loaded with an active agent, mitoxantrone, for treatment of melanomas.

Reszka does not disclose the method of claim 101 since there is no administration of drug to the CNS. Reszka also does not disclose the method of preparation of claim 102 since the nanoparticles are not loaded with an effective amount of a drug for treatment of a central nervous system disorder. As noted on page 232, mitoxantrone is an

anticancer drug for treatment of breast cancer, acute leukemia, malignant lymphomas and hepatocellular carcinoma. There is no mention of transport to the CNS – indeed, the paper teaches away from transport to the CNS, referring transport to the RES, especially the liver and spleen, at col. 2, page 232. As noted at the top of col. 1, page 233, the surfactant is used to increase blood circulation time (i.e., because it decreases uptake by the RES). One skilled in the art would be led away from the use of particles which decrease uptake, when the need is to increase transport through tissue, i.e., the blood brain barrier.

It is very clear from the data in Table 2 that the incorporation of the poloxamine into the polymer does nothing to enhance delivery to solid tumors. As stated at the top of col. 1, page 237, ***only*** coated nanoparticles produced enhanced concentrations in tumors. Applicants' claims specifically exclude coatings. Applicant's claims are drawn to uncoated polymeric nanoparticles for delivery of an effective amount of drug to the CNS, based on their finding that the incorporation of a poloxamine into (as opposed to onto the nanoparticles, in the form of a coating) greatly enhances uptake into the CNS, even of drugs that do not pass the blood brain barrier. See example 3, pages 25-26 and Figures 2-5. This is neither disclosed by nor obvious from Reszka. Reszka does not disclose a method for administering a physiologically effective compound to the central nervous system containing nanoparticles which are free of a surfactant coating. Therefore, the claims, as amended, are novel over Reszka.

b. Beck

Beck discloses polybutylcyanoacrylate (PBCA) nanoparticles which were prepared by emulsion polymerization using 1% butylcyanoacrylate monomer, 1% dextran

70 and 0.2 % polyoxamer 188 in 0.01M HCl and loaded with an active agent, then adding 1% poloxamine 1508 as a coating surfactant to the resulting suspension (page 103, lines 21-23).

Beck describes the earlier work of Reszka, et al., for delivery of mitoxantrone to solid melanoma tumors. As noted at the top of col. 1, page 103, the surfactant is used to increase blood circulation time and reduce liver uptake. The results in Table 2 and Figure 3 clearly teach away from the use of nanoparticles without a surfactant coating.

As discussed above with respect to Reszka, Beck does not disclose nanoparticles without a surfactant coating for delivery of a compound to the CNS.

The present application describes PBCA nanoparticles containing polysorbate 85 as a stabilizer or as an alternative embodiment containing a dextran stabilizer other than dextran 70, such as dextran 12000. Example 3 describes nanoparticles adsorbed with a drug which does not pass the blood brain barrier (bbb) when given systemically, the leu-enkephalin analog dalargin. Dalargin is a highly potent analgesic when injected directly into the brain, but it has no effect when given peripherally. None of the control groups (empty nanoparticles and dalargin alone) exhibited any analgesic effects in mice. However, administration of dalargin loaded polysorbate 85 nanoparticles led to increased analgesia on the hot plate (Figure 2). Beck does not disclose a method for administering a physiologically effective compound to the central nervous system containing nanoparticles which are free of a surfactant coating. Therefore, the claims, as amended, are novel over Beck.

Rejections Under 35 U.S.C. § 103

Claims 101-108, 111-122, 132 and 133 were rejected under 35 U.S.C. § 103(a) as obvious over Reszka or Beck in view of WO 95/2296 by Kreuter *et al* ("Kreuter"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Kreuter discloses the "surprising finding" that treatment of nanoparticles having a drug absorbed, adsorbed or incorporated therein with a sufficient ***coating*** of an appropriate surfactant allows the adsorbed drug to traverse the bbb (page 6, lines 13-15). Kreuter describes the preparation of PBCA nanoparticles using an acidic polymerization medium containing dextran 70000 as a stabilizer (page 14, lines 18-20). After polymerization, the nanoparticles were loaded with the drug to be delivered. Finally, the nanoparticles were coated by the addition of a 1% solution of surfactant, preferably Polysorbate 80, to the nanoparticle suspension (page 7, lines 15-17).

Kreuter describes PBCA nanoparticles loaded with dalargin, a highly potent analgesic when injected directly into the brain, but ineffective when given peripherally. Activity thresholds were measured using the tail flick test. Only dalargin absorbed to nanoparticles and coated with polysorbate 80 had an analgesic activity which became statistically significant at a dose of 5mg/kg dalargin (page 18, lines 12-15).

Reszka and Beck describe the use of drug loaded nanoparticles of PBCA with and without a surfactant coating for the treatment of leukemia and B16 melanoma. Reszka further describes the distribution of surfactant coated and uncoated nanoparticle-associated mitoxantrone in the heart, spleen, liver, serum, and bone marrow. However, Rezka and Beck do not disclose the passage of mitoxantrone across the bbb via coated or

uncoated nanoparticles. Kreuter discloses the preparation of drug-loaded nanoparticles which includes the additional step of coating the nanoparticles with a surfactant coating after polymerization and drug-loading.

None of Reszka, Beck, or Kreuter teach one of skill in the art to use nanoparticles without a surfactant coating to cross the bbb. None describe administration of a drug which is effective in the CNS.

All of Reszka, Beck and Kreuter teach surfactant coating is critical to decrease uptake by the RES.

Accordingly, one of skill in the art would not be motivated to use the claimed nanoparticulate formulation for delivery as defined by amended claim 101 and claims dependent thereon; nor to make the nanoparticulate formulation of a drug for delivery to the CNS as defined by amended claim 102 and claims dependent thereon, much less with a reasonable expectation of success.

Allowance of claims 101-108, 111-122, 132-133, and 135-136 as amended, is respectfully solicited.

Respectfully submitted,

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Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein, are being facsimile transmitted on the date shown below to the Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.

Ronna Berman

June 8, 2004
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